Late adverse effects of treatment for testicular cancer or Hodgkin's lymphoma

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SUMMARY

Hodgkin's lymphoma and testicular cancer are both rare malignancies that mainly affect young adults, but have an excellent prognosis. With growing numbers of patients surviving for decades after intensive treatment with radiation, chemotherapy or both, it has become increasingly clear that these treatments can cause severe late adverse effects, even after very long-term follow-up. This thesis focused on the long-term risk of second primary malignancies and cardiovascular disease a long time after treatment for Hodgkin's lymphoma and testicular cancer.

The main questions of this thesis are:

- Is the risk of cardiovascular diseases increased in 5-year survivors of testicular cancer, compared with the risk in the general population and compared between different treatments?
- What are the differences between treatments in the risk of developing a serious late treatment effect, i.e., a second cancer or a cardiovascular disease, in 5-year survivors of testicular cancer?
- Do testicular cancer patients have an increased risk of leukemia compared with the general population, especially after etoposide-containing chemotherapy?
- Which late effects of radiotherapy and chemotherapy have an impact on the life expectancy of young Hodgkin's lymphoma patients?
- Is the risk of specific cardiovascular diseases increased in 5-year survivors of Hodgkin's lymphoma (diagnosed before age 41), compared with the risk in the general population and compared between different treatments?
- What are the risk factors for the increased incidence of stomach cancer among testicular cancer and Hodgkin's lymphoma survivors?

The unique nation-wide registry of the former Committee of Testicular Tumors was supplemented for the research among testicular cancer patients resulting in a total of approximately 2,700 testicular cancer patients. The study among Hodgkin 's lymphoma patients included approximately 1,500 Hodgkin's lymphoma patients who had been treated in the Netherlands Cancer Institute in Amsterdam or the Erasmus Medical Center in Rotterdam. Both patient groups were diagnosed in the period 1965-1995 and followed for almost 20 years.

Chapter 2 describes the long-term risk of cardiovascular diseases among 2,512 5-year survivors of testicular cancer who were treated between 1965 and 1995. After a median follow-up of 18.4 years, 694 cardiovascular events occurred, including 141 acute myocardial infarctions (MIs). The risk of coronary heart disease was 1.2-fold increased compared with the general population, yielding 14 excess cases per 10,000 person-years over and above the expectation based on rates in the general population. In the general population with a similar age distribution 82 coronary heart diseases per 10,000 persons per year would have been expected, whereas among our 5-year survivors of testicular cancer 96 coronary heart diseases per 10,000 persons per year developed. Nonseminoma survivors with attained ages of less than 45 years had a 2.1-fold increased risk of MI, nonseminoma survivors with attained ages of 45 to 54 years old had a 1.9-fold increased risk of MI, whereas survivors with attained ages of 55 years or older had a significantly decreased risk (relative risk = 0.53) compared with the general population. Mediastinal irradiation was associated with a 3.7-fold increased risk of MI compared with surgery alone, whereas infradiaphragmatic irradiation was not associated with an increased MI risk. After cisplatin, vinblastine and bleomycin (PVB) chemotherapy the risk of MI was 1.9-fold increased and the risk of cardiovascular disease was 1.5-fold increased risk, whereas after bleomycin, etoposide and cisplatin (BEP) chemotherapy the risk of MI was not significantly 1.2-fold increased, compared with the risk after surgery only. Recent smoking was associated with a 2.6-fold increased risk of MI.

It can be concluded that nonseminomatous testicular cancer survivors have a moderately increased risk of myocardial infarction at young ages. Physicians should be aware of excess risk of cardiovascular disease associated with mediastinal radiotherapy, PVB chemotherapy, and recent smoking. It is especially important in testicular cancer survivors that modifiable cardiovascular risk factors, such as hypertension, hypercholesterolemia and diabetes, are adequately treated. Whether BEP chemotherapy increases the risk of cardiovascular disease should be evaluated after more prolonged follow-up.

In chapter 3 we compared radiotherapy and chemotherapy effects on the long-term risks of developing second malignancies and cardiovascular diseases in our nationwide cohort comprising 2,707 five-year testicular cancer survivors. Until then, studies only evaluated the risk of one late effect of treatment at a time. We estimated the risk to develop either a cardiovascular disease or a second malignancy simultaneously, because radiotherapy and chemotherapy

can cause different adverse effects. This enables oncologists to better weigh the risks of different treatments, because for testicular cancer there are different, equally effective treatment options available.
After a median follow-up time of 17.6 years, 270 TC survivors developed second malignancies. The risk of developing any second malignancy other than testicular cancer was 1.7-fold increased, with 32.3 excess malignancies per 10,000 person-years, compared with the general population.
Mediastinal radiation was associated with a strongly increased risk of cardiovascular disease. Subdiaphragmatic radiotherapy increased the risk of second malignancies 2.6-fold compared with the general population, especially stomach, pancreatic or bladder cancer. Patients irradiated for nonseminoma had a higher risk of second malignancies than patients irradiated for seminoma. Because nonseminoma patients were irradiated with higher doses than seminoma patients, this suggests that the risk of second malignancies is higher after higher radiation doses.
Subdiaphragmatic radiotherapy did not increase the risk of cardiovascular disease. Cisplatin-containing chemotherapy was associated with a 1.7-fold increased risk of cardiovascular disease and a 2.1-fold increased risk of second malignancies, compared with surgical treatment alone.
The risk of developing a severe late treatment effect like a second malignancy or cardiovascular disease after testicular cancer is about 1.8-fold increased after subdiaphragmatic radiotherapy or after cisplatin-containing chemotherapy, compared with surgical treatment alone. This risk is similar to the risk of smoking. The risks of a second malignancy and cardiovascular disease remained increased for more than 25 years after diagnosis. The median survival was 1.4 years after a second malignancy and 4.7 years after a cardiovascular disease. Prolonged follow-up after chemotherapy is needed to reliably compare the late complications of radiotherapy and chemotherapy after 20 years.

In chapter 4 we describe a nationwide study on the risk of leukemia and the myelodysplastic syndrome after treatment among 3,458 patients diagnosed with testicular cancer between 1965 and 1995. To be sure no leukemias were missed, the cause of death was obtained from Statistics Netherlands for all patients who died. Eleven patients developed leukemia or myelodysplastic syndrome. The risk of leukemia was 2.0-fold increased compared with the general population resulting in 1.1 excess cases per 10,000 person-years. Leukemia risk was not associated with type and doses of standard chemotherapy regimens used in the treatment of testicular cancer, like PVB (cisplatin,

vinblastine and bleomycin) and BEP (bleomycin, etoposide and cisplatin). The mean interval between the diagnosis of testicular cancer and leukemia was 8.5 years. Eighty percent of the patients who developed leukemia or myelodysplastic syndrome died after a mean time of 3.9 years. In conclusion, risk of leukemia or myelodysplastic syndrome is not a major problem among testicular cancer patients treated with standard BEP chemotherapy.

Chapter 5 describes the mortality in a cohort of 1,261 Hodgkin's lymphoma patients treated before age 41 in the period 1965 until 1987. After a median follow-up duration of 17.8 years, 534 patients died. The main cause of death among Hodgkin's lymphoma patients was Hodgkin's lymphoma (55% of all deaths), but after 20 years, mortality from Hodgkin's lymphoma was negligible. The relative risks and absolute excess risks of death from second primary cancers and cardiovascular diseases continued to increase after 10 years. From 10 years after diagnosis, the risk of death from causes other than Hodgkin's lymphoma exceeded the risk of death from Hodgkin's lymphoma. Even more than 30 years after diagnosis, Hodgkin's lymphoma patients still had a five-fold increased risk of death from all causes other than Hodgkin's lymphoma compared to the general population. Consequently, 30 years after diagnosis, 192 excess deaths from solid tumors and 27 excess deaths from cardiovascular disease occurred per 1,000 patients per year, compared with the number of deaths in the general population. The risk of death from second primary cancers and cardiovascular diseases was especially increased in patients treated before age 21, but these risks seemed to abate with age.

In chapter 6 we compared the incidence of cardiovascular diseases with that in the general population and between different treatment groups in our cohort of 1,486 five-year survivors of Hodgkin's lymphoma. All patients were treated in the Netherlands Cancer Institute or the Erasmus Medical Center – Daniel den Hoed Cancer Center and diagnosed before age 41 in the period 1965 through 1995. The treatment included radiotherapy for 95% of the patients, of whom 85% were irradiated to the mediastinum.
The risks of several cardiovascular diagnoses were 3- to 5-fold increased in Hodgkin's lymphoma survivors compared with the general population. After a median interval of 19 years 36 excess patients developed myocardial infarctions, 50 excess patients developed angina pectoris and 26 excess patients developed heart failure per 10,000 patient years compared with the general population.
The already increased risk of heart failure after mediastinal radiotherapy was

2.8-fold further increased by anthracyclines and the increased risk of valvular disorders was 2.1-fold further increased by anthracyclines. Even after 25 years the risk was still increased, leading to increasing absolute excess risks over time; after 25 years 70 excess patients developed a myocardial infarction, 208 excess patients developed angina pectoris and 63 excess patients developed heart failure per 10,000 patient-years, compared with the numbers in the general population. The cumulative risk of heart failure or cardiomyopathy after mediastinal irradiation and anthracyclines was 8% after 25 years.

In chapter 7 we evaluated the roles of radiation dose, chemotherapy and other factors in the etiology of stomach cancer in a multicenter cohort study of 5,142 long-term survivors of testicular cancer or Hodgkin lymphoma treated in the Netherlands between 1965 and 1995. Subsequently, we conducted a nested case-control study comprising 42 patients with stomach cancer and 126 matched controls. Detailed information on treatment, smoking, gastro-intestinal diseases and family history was collected. We estimated the mean radiation dose to the stomach for each subject. The risk of developing stomach cancer after testicular cancer or Hodgkin's lymphoma was 3.4-fold increased compared with the risk in the general population. The risk was strongly radiation dose-dependent, yielding a 10-fold increased risk after stomach doses above 20 Gy as compared with stomach doses below 11 Gy. Mean stomach doses above 20 Gy were observed in patients with Hodgkin's lymphoma whose radiation fields included the spleen and in testicular cancer patients who underwent multiple irradiations. Irradiation to the para-aortic lymph nodes with 30 Gy leads toa mean stomach dose of 10.1 Gy. Results were suggestive for an increased risk of stomach cancer after high doses of procarbazine. The risk was 5.4-fold increased after 13,000 mg or more compared with less than 10,000 mg procarbazine (median number of cycles was 6, with a median dose of 11,550 mg). The role of chemotherapy in the development of stomach cancer should be further examined, because the numbers of patients treated with chemotherapy alone were still relatively small.

CONCLUSION

Over the past decades, the introduction of combination chemotherapy and modern radiation techniques, patients with Hodgkin's lymphoma or testicular cancer have obtained an ever more favourable prognosis. Nowadays, over 90%

of testicular cancer patients and approximately 80% of Hodgkin's lymphoma patients survive. However, the results of this thesis indicate that both irradiation and chemotherapy are associated with long-term increased risks of second malignancies and cardiovascular disease. These serious late treatment effects can have a major impact on the survivors' quality of life and can even cause death. The implications of the results of this thesis are different for survivors and for recently treated, current or future patients. Patients who have been treated for Hodgkin's lymphoma or testicular cancer at least 10 years ago should undergo regular surveillance by their oncologist or general practitioner, depending on their treatment.

The following recommendations can be made:

– After mediastinal irradiation:
  - Screening, and treatment if necessary, of cardiovascular risk factors, such as hypercholesterolemia, hypertension, hypothyroidism, hyperthyroidism and diabetes. Advise to exercise regularly, to maintain a healthy body weight and to refrain from smoking.
  - Females: Yearly screening for breast cancer.
– After subdiaphragmatic irradiation:
  - Oncologists, general practitioners and survivors themselves should be alert to complaints that could indicate cancer, especially of the stomach, pancreas, urinary bladder or kidneys.
– After chemotherapy for testicular cancer (until 1985 PVB, BEP afterwards) or anthracylin-containing chemotherapy for Hodgkin's lymphoma:
  - Screening, and treatment if necessary, of cardiovascular risk factors, such as hypercholesterolemia, hypertension and diabetes.
  - Advise to exercise regularly, to maintain a healthy body weight and to refrain from smoking.

The risks of second malignancies and cardiovascular disease for recently treated, current and future Hodgkin's lymphoma and testicular cancer patients will probably be less pronounced than the risks described in this thesis. Increasing knowledge of late adverse effects of radiation and chemotherapy has led to smaller numbers of patients treated with radiation. Moreover, lower radiation doses and smaller radiation fields are now used if possible. Furthermore, also chemotherapic treatment consists of other cytostatic agents with less adverse effects. On the other hand new agents with yet unknown late effects are added to chemotherapic treatments.

Since long-term survival and late adverse treatment effects only occur a long time after treatment and sometimes even after dismissal from surveillance, it is

important to follow-up patients over time and to accurately document their treatment details. Only then it is possible to monitor long-term survival and late adverse effects of adapted treatment strategies, to develop treatment regimens that are as effective and as safe as possible.

In both patient populations it remains important to perform further research on the mechanisms of several cytostatic agents in the development of cardiovascular disease and stomach cancer, to enable prevention or mitigation of the development of these late adverse effects.

Current and future Hodgkin's lymphoma and testicular cancer patients should be informed about possible long-term risks of their treatment. This can influence the treatment choice when several treatment options are available, as in low stage testicular cancer (both seminoma and nonseminoma). For low stage testicular cancer patients surgical treatment with regular surveillance only is preferable. For Hodgkin's lymphoma or higher stage testicular cancer patients who need radiotherapeutic and/or chemotherapeutic treatment to be cured from their disease, it is worthwhile to adhere to the above mentioned recommendations for screening and life style advice for survivors.